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UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

Case No. 13-md-2452-AJB-MDD

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT BASED ON PREEMPTION

Date: To be determined
Time: To be determined
Courtroom:
Judge: Hon. Anthony J. Battaglia
Magistrate: Hon. Mitchell D. Dembin

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INTRODUCTION

Four years ago, this Court found clear evidence that the FDA would have rejected the addition of pancreatic cancer warnings to the package inserts of sitagliptin (a DPP-4 inhibitor), exenatide (a GLP-1 receptor agonist), and liraglutide (also a GLP-1 receptor agonist)—the three medications at issue in this multi-district litigation. The Court therefore dismissed all of plaintiffs' claims, holding:

- The doctrine of impossibility preemption presents a legal question for judges to decide, rather than a factual determination reserved for juries;[1]
- The FDA "specifically considered"[2] and "actively investigated"[3] pursuant to its Congressionally-delegated authority[4] whether exposure to these medications causes an increased risk of pancreatic cancer;
- Based on the FDA's comprehensive analysis, the Agency concluded in February 2014 that "assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are ***inconsistent with the current data***" and "the current knowledge is ***adequately reflected in the product information or labeling***;"[5] and
- The FDA's continuing assessment of relevant scientific data has not changed the Agency's judgment, based on applicable regulatory requirements, that the data do not support addition of pancreatic cancer warnings to the labels of these products.[6]

The United States Court of Appeals for the Ninth Circuit did not disagree with these determinations, but held that the Court should consider so-called "new safety

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1 *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d 1108, 1114 (S.D. Cal. 2015).
2 *Id.* at 1112.
3 *Id.* at 1121.
4 *Id.* at 1126.
5 *Id.* at 1122 (emphases added); *see also* Amy G. Egan et al., *Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment* ("FDA Assessment"), N. Engl. J. Med. 370:9 at 796 (Feb. 2014) (emphases added) (attached as Ex. A to the Declaration of Paul E. Boehm ("Boehm Decl.")).
6 142 F. Supp. 3d at 1121, 1123.

information" and permit supplemental fact discovery concerning: (1) foreign regulatory materials, and (2) source files related to spontaneous adverse event reports. Those materials have been produced—together with several million additional pages of documents plaintiffs requested—bringing the collective volume of defendants' productions in this litigation to more than 37 million pages, 92 custodial files, and more than 2,300 gigabytes of additional raw data.

Nothing has changed to warrant a different conclusion. The United States Supreme Court has confirmed that preemption is a legal question for judges to decide. *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019). And the factual record supporting preemption has only grown more compelling. Since 2015, the FDA has considered and approved labels for four additional incretin-based therapies, expanded indications for others, and approved more than 50 additional label changes for the medications at issue in this MDL—all without requiring a pancreatic cancer warning. Despite the FDA's ability to mandate label changes and its stated intent to "continue to investigate" the relationship between incretin-based therapies and pancreatic cancer, the Agency has not required any of the medicines at issue to mention, let alone warn about any risk of, pancreatic cancer in their labels.

Meanwhile, after persuading the Ninth Circuit to reinstate those portions of Dr. Fleming's (plaintiffs' regulatory expert) report stricken by this Court, plaintiffs proceeded to withdraw those sections entirely, leaving the expert record on preemption exactly as it was in 2015—no expert for plaintiffs is willing or able to say that the "new safety information" plaintiffs argue was "missing" or otherwise not considered by the FDA is material to the FDA's conclusions. The uncontroverted evidence is to the contrary, and Dr. Fleming agreed under oath that "it would be a little absurd" for the FDA to approve a pancreatic cancer warning in light of its conclusions that the scientific evidence is "inconsistent" with a causal association.[7]

[7] G. Alexander Fleming, M.D. Deposition Tr. (May 22, 2015) at 201:21–202:1 (relevant portions attached as Ex. B to Boehm Decl.).

FACTS

Today, as in 2015, the undisputed facts provide clear evidence that the FDA would reject a pancreatic cancer warning for these products:

1. This MDL proceeding involves medications approved by the FDA for the treatment of type 2 diabetes—sitagliptin (Januvia/Janumet), exenatide (Byetta/Bydureon), and liraglutide (Victoza). Plaintiffs' claims are premised on the allegation that defendants failed to warn about their respective medications' purported risk of pancreatic cancer.

2. Sitagliptin belongs to a class of medications referred to as DPP-4 inhibitors. Exenatide and liraglutide belong to a class of medications referred to as GLP-1 receptor agonists. These two classes of medication, DPP-4 inhibitors and GLP-1 receptor agonists, sometimes are collectively referred to as "incretin-based therapies" because—notwithstanding their different mechanisms of action—each class involves incretin hormones, which operate in the body to lower blood sugar by stimulating or sustaining production of insulin.

3. More than 34 million people in the United States alone, more than 1 out of 10 Americans, suffer from type 2 diabetes.[8] Different treatment options need to be available for individuals with type 2 diabetes because, given the chronic nature of the disease, patients often require a variety of options and/or a combination of medications over time to control their blood sugar.

4. Incretin-based therapies are an approved treatment option for patients with type 2 diabetes. All leading medical organizations in the diabetes field recommend them, including, in particular, for patients with (or at high risk for) heart disease, those with established kidney disease, and those at high risk for

[8] *See* American Diabetes Association, *Statistics About Diabetes*, *available at* https://www.diabetes.org/resources/statistics/statistics-about-diabetes (attached as Ex. C to Boehm Decl.).

hypoglycemia or weight gain.[9]

5. Under the federal Food, Drug, and Cosmetic Act ("FDCA"), Congress has committed regulatory authority over the approval and sale of prescription medications to the FDA, including considerable authority over the content of prescription medication labeling. 21 U.S.C. § 355(d), (o); 21 C.F.R. pt. 201. Pharmaceutical manufacturers, or sponsors, must submit proposed labeling to the FDA as part of the new drug-approval process. *See* 21 C.F.R. § 314.50. Securing initial FDA approval of a new drug is predicated, in part, on a manufacturer's use of FDA approved product labeling and package inserts. *Id.*; 21 C.F.R. § 314.105(b).

6. When the FDA has approved incretin-based medicines as safe and effective, the Agency necessarily has also approved the labeling, including warnings and adverse reactions, for the medications.

7. The FDA has its own, independent statutory obligation to ensure that labels reflect the most recent medical science. The Food and Drug Administration Amendments Act of 2007 (FDAAA) requires the FDA to inform manufacturers when the Agency "becomes aware of new information, including any new safety information . . . that . . . should be included in the label of the drug,"[10] and gives the Agency broad authority to order any labeling changes it believes are necessary.[11] In July 2013, the FDA issued a new guidance addressing the impact of FDAAA on the implementation of safety labeling changes for prescription medications.[12] In the

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[9] *See generally* American Diabetes Association, *9. Pharmacologic Approaches to Glycemic Treatment*: Standards of Medical Care in Diabetes—2020, Diabetes Care (Jan. 2020), *available at* https://care.diabetesjournals.org/content/43/Supplement_1/S98 (attached as Ex. D to Boehm Decl.).

[10] 21 U.S.C. § 355(o)(4)(A); *see* 21 U.S.C. § 355(o)(3)(C).

[11] *See* FDA, Center for Drug Evaluation and Research, *Guidance for Industry: Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act* (July 2013), *available at* https://www.fda.gov/media/116594/download (attached as Ex. E to Boehm Decl.).

[12] *See id.* (Ex. E).

guidance, the FDA notes that "the definition of new safety information [under the Act] is broad [enough] to enable FDA to require application holders to add information about serious risks to the labeling of a drug when the Agency determines that such information should be included."[13]

8. In general, if a manufacturer wants to amend its labeling post-marketing, it must first obtain FDA approval through the submission of a "prior approval supplement" ("PAS").[14] The regulations, however, include a limited exception to the "prior approval" requirement by which manufacturers can add or strengthen a warning through a "changes being effected" (CBE) to reflect "newly acquired information" about the product's safety.[15] The FDA will review the contents of the CBE and the amended labeling under the same standard applied for a PAS, and will retroactively reject the CBE if it does not find that "the evidence of a causal association satisfies the standard for inclusion in the label."[16]

9. "Newly acquired information" under the CBE regulation includes "data, analyses, or other information not previously submitted to the [FDA], which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to the FDA."[17] In addition, "newly acquired information" "must provide reasonable evidence of a causal association" of a "clinically significant" risk or hazard linked to a drug."[18] Federal law does not permit a manufacturer to warn of suspected risks or to identify adverse reactions that are not scientifically substantiated.

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[13] *Id.* (Ex. E) at 4.
[14] *See* 21 C.F.R. § 314.70(b).
[15] *See id.* § 314.70(c)(6)(iii); *see also Albrecht*, 139 S. Ct. at 1673.
[16] 21 C.F.R. § 314.70(c)(6)(iii)(A).
[17] 21 C.F.R. § 314.3 (emphases added).
[18] 21 C.F.R. § 201.57(c)(6)(i) (emphasis added).

10. Federal law, through the FDA, imposes this standard "to prevent over-warning so that less important information does not overshadow more important information . . . [and to] exclude exaggeration of risk, or inclusion of speculative or hypothetical risks that could discourage appropriate use of a beneficial drug.'" *Albrecht*, 139 S. Ct. at 1673 (quotation marks and citation omitted) (emphasis added).

11. To ensure that labeling promotes federal safety goals, the FDA restricts what may be included in labeling:

- "Labeling is not intended to be a dispositive treatise of all possible data and information about a drug."[19]
- Inclusion of "substantial differences of opinion among experts" or "other serious medical controversies" concerning labeling statements "would result in uncertainty and confusion, and, accordingly, decrease the usefulness of the warnings in protecting the public."[20]
- Inclusion in "drug labeling of medical or scientific controversy concerning labeling would be highly confusing, and thus misleading, in violation of section 502(a) of the act."[21]

12. FDA approval of incretin-based therapies has never been conditioned on labeling that includes a pancreatic cancer warning,[22] nor has the FDA ever required

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[19] Labeling and Prescription Drug Advertising: Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,441 (June 26, 1979).

[20] *Id*. at 37,448.

[21] *Id*. at 37,455.

[22] FDA approved Byetta (exenatide) in 2005; Januvia (sitagliptin) in 2006; Janumet (sitagliptin and metformin) in 2007; Onglyza (saxagliptin) in 2009; Victoza (liraglutide) in 2010; Tradjenta (linagliptin) in 2011; Bydureon (exenatide) in 2012; Nesina (alogliptin) in 2013; Bydureon pen (exenatide extended release); Tanzeum (albiglutide), Trulicity (dulaglutide), and Saxenda (liraglutide) in 2014; Adlyxin (lixisenatide) in 2016; Bydureon BCise (exenatide extended release) and Ozempic (semaglutide) in 2017; and Rybelsus (oral semaglutide) in 2019. The FDA Approval Letters for Byetta, Januvia, Janumet, Onglyza, Victoza, Tradjenta, Bydureon, Nesina, Bydureon pen, Tanzeum, Trulicity, Saxenda, Adlyxin,

such warning pursuant to its obligations and authority under FDAAA.

13. The FDA has monitored the pancreatic safety of incretin-based therapies, and specifically the risk of pancreatic cancer, for many years. On September 17, 2009, the FDA Division of Metabolic and Endocrine Products asked the FDA Office of Surveillance and the Epidemiology Division of Pharmacovigilance to review its adverse event reporting database for cases of pancreatic cancer in Januvia and Byetta users.[23] To do so, the Epidemiology Division searched the database and conducted a literature review using the National Health Institute database of publications.[24] The FDA concluded that "little inference for risk [could be] appreciated from review of spontaneous reports of pancreatic cancer in adult recipients of anti-diabetics agents," because pancreatic cancer is "relatively common" in adults.[25]

14. After academic researchers at UCLA theorized that incretin-based therapies might cause pancreatic cancer, the FDA announced in March 2013 that it would conduct a comprehensive evaluation of that issue.[26] The FDA said that it would consider the totality of available scientific data, as well as the Agency's own "further investigat[ion] [into the] potential pancreatic toxicity associated with the incretin mimetics." The FDA said that upon completion of that evaluation it would

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Bydureon BCise, Ozempic, and Rybelsus (attached as Exs. F through U, respectively, to Boehm Decl.).

[23] *See* Memorandum from John Bishai, Ph.D., Regulatory Project Manager, FDA, DMEP, to Millie Wright, FDA, Office of Safety and Epidemiology ("Bishai Memorandum") (Sept. 17, 2009) (attached as Ex. V to Boehm Decl.).

[24] *See* Memorandum from Allen Brinker, Team Leader, FDA Div. of Pharmacovigilance 1, to Mary Parks, Dir., FDA Div. of Metabolism & Endocrinology Prods., at 2 (Dec. 10, 2009) (attached as Ex. W to Boehm Decl.). Both this memorandum and the memorandum from Dr. Bishai were obtained in response to a Freedom of Information Act request made to FDA.

[25] *Id*. (Ex. W) at 8.

[26] FDA, *FDA Drug Safety Communication: FDA Investigating Reports of Possible Increased Risk of Pancreatitis and Pre-Cancerous Findings of the Pancreas from Incretin Mimetic Drugs for Type 2 Diabetes* (Mar. 14, 2013) ("FDA Review Announcement") (attached as Ex. X to Boehm Decl.).

"communicate its final conclusions and recommendations."[27] In the meantime, the FDA stated that it "ha[d] not concluded these [drugs] may cause or contribute to the development of pancreatic cancer," and it advised doctors in bold print that they "should continue to follow the prescribing recommendations in the drug labels."[28]

15. On February 27, 2014, the FDA announced that its "comprehensive evaluation[]" was "now complete." The Agency "communicate[d] its final conclusions and recommendations" in a joint publication with the European Medicines Agency ("EMA") and Dutch Medicines Evaluation Board entitled "Pancreatic Safety of Incretin-Based Drugs: FDA and EMA Assessment" in *NEJM*, the oldest peer-reviewed medical journal in the United States.[29]

16. The FDA Assessment describes the "comprehensive evaluations" independently conducted by the FDA and EMA and concludes:

> Thus, the FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that ***assertions concerning a causal association between incretin-based drugs and*** pancreatitis or ***pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data***.[30]

17. The FDA also concluded:

> The FDA and the EMA believe that the ***current knowledge is adequately reflected in the product information or labeling*** . . . .[31]

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[27] *Id*. (Ex. X).
[28] *Id*. (Ex. X).
[29] FDA Assessment (Ex. A) at 795. The article was "updated" (with no changes to the conclusions) on June 5, 2014. *See Corrections*, N. Engl. J. Med. 370:23 (June 2014) (attached as Ex. Y to Boehm Decl.).
[30] FDA Assessment (Ex. A) at 796 (emphases added).
[31] *Id.* (Ex. A) (emphasis added).

18. The FDA exercised congressionally-delegated authority in undertaking, conducting, and publishing the results of its comprehensive investigation.[32] Congress has delegated authority to the FDA both (i) to determine whether new safety information warrants a labeling change, and pursuant to which the FDA undertook its evaluation of incretin-based therapies,[33] and (ii) to "establish and make publicly available clear written polices to . . . govern the timely submission, review, clearance, and disclaimer requirements for articles."[34]

19. The FDA prepared its Assessment as an "FDA-Assigned" article and without the disclaimer that is required when "the views expressed in the article or speech do not necessarily represent the official views or policies of the agency."[35]

20. After publishing the results of its comprehensive evaluation in the *New England Journal of Medicine*, the FDA reaffirmed that it would not approve a pancreatic cancer labeling change for incretin-based therapies.

21. On March 25, 2014, the FDA denied Public Citizen's petition asking the Agency to withdraw Victoza from the market, based in part on a claim that patients being treated with the medication faced an increased risk of pancreatic cancer.[36] Noting that it had "carefully considered the information submitted in the Petition, the comments submitted to the docket, and other data identified by the Agency,"[37] the FDA denied the Petition. As to pancreatic cancer, the FDA found that the data offered

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[32] 142 F. Supp. 3d at 1126.

[33] 21 U.S.C. § 355(o)(4).

[34] 21 U.S.C. § 379d-2(b).

[35] *See* FDA Staff Manual Guide 2126.3, Review of FDA-Related Articles and Speeches § 6.A (attached as Ex. Z to Boehm Decl.); *see also* Fleming Tr. (Ex. B) at 84:22–84:25 ("Q: You do not in any way dispute that these are the conclusions of the FDA; is that fair? A: No. I agree. This represents FDA's position.").

[36] *See* Letter from Janet Woodcock, Dir., FDA Center for Drug Evaluation and Research, to Drs. Elizabeth Barbehenn and Sidney Wolfe, Public Citizen's Health Research Group (March 25, 2014) ("Public Citizen Letter") at 26 (attached as Ex. AA to Boehm Decl.).

[37] *Id.* (Ex. AA) at 1.

"no new evidence regarding the risk of pancreatic carcinoma . . . that would support *any changes to the current approved labeling*."[38]

22. The FDA again considered the safety and efficacy of incretin-based therapies in late 2014 when it convened an Advisory Committee to consider approval of Saxenda, a higher dose of liraglutide for use in weight management. In a Briefing Book provided for the Committee, the FDA concluded: "Risk for pancreatic cancer has more recently emerged as a concern with GLP-1-based therapies, including liraglutide. . . . However, ***animal, observational, and clinical trial data reviewed by FDA to date have not supported a causal association***."[39] Referring to its February 2014 Assessment, the FDA added: "Both FDA and the European Medicines Agency (EMA) have explored multiple data streams to evaluate pancreatic toxicity as a potential drug safety signal, which to date, ***do not support pancreatic cancer as an incretin mimetic-mediated event***."[40]

23. Since February 2014, the FDA has approved at least eight new incretin-based therapies—Bydureon pen (2014), Tanzeum (2014), Trulicity (2014), Saxenda (2014), Adlyxin (2016), Bydureon BCise (2017), Ozempic (2017), and Rybelsus (2019)—all without a pancreatic-cancer warning.

24. In July 2017, the FDA convened an Advisory Committee to evaluate a proposed new cardiovascular risk reduction indication for liraglutide based on the data from the LEADER study. In advance of the meeting, the FDA prepared a Briefing Book, which included a detailed summary of the FDA's review and evaluation of the pancreatic safety of Victoza and other incretin-based therapies. The FDA also conducted a dedicated oncology review of the pancreatic cancer data and included the findings from that review in the Briefing Book.

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[38] *Id.* (Ex. AA) at 26 (emphasis added).

[39] FDA Briefing Document, NDA 206321 Liraglutide Injection, 3 mg, Endocrinology and Metabolic Drugs Advisory Committee Meeting, (Sept. 11, 2014) at 117 (attached as Ex. AB to Boehm Decl.) (emphasis added).

[40] *Id*. (Ex. AB) at 313 (emphasis added).

25. The Agency's review "did not identify overt pancreatic toxic effects from exposure to GLP-1 RAs" and found instead that the clinical data "were inconclusive and not sufficiently compelling to support incorporation of changes regarding the potential pancreatic cancer signal in product labeling."[41] The FDA also concluded that, "taking into consideration the totality of information available, the additional information provided in LEADER does not appear to substantively alter the original FDA and EMA conclusions regarding the lack of sufficient information to conclusively determine whether long term exposure to GLP-RAs increase the risk of pancreatic cancer."[42]

26. On August 25, 2017, after the Advisory Committee meeting was held, the FDA approved an expanded indication for Victoza, to "reduce risk for major adverse cardiovascular events, myocardial infarction, stroke and cardiovascular disease in adults with type 2 diabetes and established CVD"[43] without including any information about pancreatic cancer in the labeling.

27. The FDA has approved nearly 100 labeling changes for the medications at issue in this MDL since the initial approvals of these products. None of these labeling updates has included a pancreatic cancer warning. For sitagliptin (Januvia and Janumet), the FDA has approved 36 labeling changes since initial approval, most recently in August 2019.[44] The FDA has approved 47 labeling updates for exenatide (Byetta and Bydureon) since it was approved, most recently in February 2020.[45] The

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[41] FDA Briefing Document for NDA 022341, Endocrinology and Metabolic Drugs Advisory Committee Meeting (June 20, 2017) ("FDA June 2017 Briefing Document"), at 129 (attached as Ex. AS to Boehm Decl.).

[42] *Id.* (Ex. AS) at 133.

[43] FDA Label Updates for Victoza, dated August 2017 (attached, with other label updates, as Ex. AC to Boehm Decl.).

[44] *See* FDA Label Updates for Januvia and Janumet (attached collectively as Ex. AD to Boehm Decl.).

[45] *See* FDA Label Updates for Byetta and Bydureon (attached collectively as Ex. AE to Boehm Decl.).

FDA has approved 12 labeling updates for liraglutide (Victoza) since it was approved, most recently on June 17, 2019, expanding the approved use of Victoza to pediatric patients 10 years or older, making it the first non-insulin drug approved to treat type 2 diabetes in children since metformin in 2000.[46] In expanding the indication, the FDA stated that it "encourages drugs to be made available to the widest number of patients possible when there is evidence of safety and efficacy."[47]

29. In total, the FDA now has approved five DPP-4I and eleven GLP-1RA medications for treatment of type 2 diabetes in the United States and reviewed the labeling for these medications hundreds of times over the past 15 years. The FDA never has required the labeling of any of these products to include a pancreatic cancer warning, as it would have been obligated to do under the FDAAA if the Agency believed there was "reasonable evidence of a causal relationship" between incretin-based therapies and pancreatic cancer.

PROCEDURAL BACKGROUND

In June 2014, the Court denied without prejudice defendants' summary judgment motion based on preemption to permit plaintiffs to pursue further discovery. Plaintiffs completed that discovery, and defendants moved for summary judgment again on June 19, 2015. On November 9, 2015, this Court granted defendants' motion:

> Despite the high burden imposed on a preemption proponent, the unprecedented facts of this case cross the clear evidence threshold, making Defendants' preemption defense not only viable, but also dispositive of Plaintiffs' failure-to-warn claims. . . . Defendants have demonstrated by clear evidence that the FDA would have rejected a reference to pancreatic

[46] *See* FDA Label Updates for Victoza (Ex. AC).

[47] *See* Press Release, FDA, "FDA approves new treatment for pediatric patients with type 2 diabetes" (June 17, 2019), https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pediatric-patients-type-2-diabetes (statement of Lisa Yanoff, M.D., acting director of the Division of Metabolism and Endocrinology Products) (attached as Ex. AF to Boehm Decl.).

> cancer in the product labeling during the time in which Plaintiffs' claims accrued. Plaintiffs' challenges to the FDA's conclusions regarding pancreatic cancer risk are insufficient to overcome preemption in light of the extensive regulatory history of the drugs at issue. ***The evidence establishes the FDA has reviewed the risk specific to Plaintiffs' claims and, after considering the totality of available scientific data, concluded a warning or other reference to that risk is unsubstantiated***.

In re Incretin-Based Therapies Prods. Liab. Litig., 142 F. Supp. 3d 1108, 1112, 1132 (S.D. Cal. 2015) (emphasis added). The Court also concluded that the undisputed facts in this case "establish the FDA has considered pancreatic cancer risk, the specific issue Plaintiffs allege Defendants should have warned of or otherwise referenced in their product labeling," and "consistently concluded that a causal association between the drugs and pancreatic cancer is indeterminate." *Id.* at 1120–24. These actions, the Court explained, "fall[] squarely within the FDA's congressionally delegated authority to regulate the safety of prescription drugs . . . [and] exemplif[y] the FDA's approach in discharging its regulatory duties." *Id.* at 1126. In granting judgment in favor of defendants, the Court rejected plaintiffs' insistence that a sponsor cannot establish preemption absent express rejection of a proposed labeling change, observing that the "FDA's review of pancreatic safety was ***more thorough*** than a review of relevant data offered in connection with a CBE or PAS." *Id.* at 1124–25 (emphasis added).

Plaintiffs appealed. In December 2017, the Court of Appeals for the Ninth Circuit reversed and remanded.[48] The Ninth Circuit "d[id] not decide whether the defendants met their burden under *Wyeth*'s 'clear evidence' test," but directed the Court to (1) consider the materiality of the so-called "new safety information" and (2) permit discovery into source files related to spontaneous adverse event reports and foreign regulatory files.[49] The Ninth Circuit also held that the Court should not have

[48] *See In re Incretin-Based Therapies Prod. Liab. Litig.*, 721 F. App'x 580 (9th Cir. 2017).

[49] *Id.* at 581–84.

partially disqualified plaintiffs' expert, Dr. Alexander Fleming, based on a conflict of interest and violations of the protective order.[50]

On remand, the Court ordered defendants to produce the documents identified by the Ninth Circuit as well as to update previous productions and produce additional custodial files identified by plaintiffs. *Id.* Defendants' supplemental productions and additional depositions are now complete.

As for Dr. Fleming, plaintiffs withdrew the very opinions related to materiality that they had asked the Ninth Circuit to reinstate. Accordingly, Dr. Fleming does not offer an opinion that the "newly acquired information" plaintiffs point to would have been material to the FDA, nor does any other expert put forward by plaintiffs.[51] The only expert testimony on that subject is from defendants' expert, Dr. Lawrence Goldkind, whose unrebutted testimony is that the materials plaintiffs point to are immaterial and would not have altered the FDA's conclusion that the scientific data do not support a pancreatic cancer warning in the labeling of incretin-based therapies.[52]

LEGAL STANDARD FOR PREEMPTION

The Supreme Court confirmed in 2019 that preemption is a question of law for a court, not a jury, to consider. *Albrecht*, 139 S. Ct. at 1679–80. Preemption analysis "involves the use of legal skills to determine whether agency disapproval fits facts that are not in dispute." *Id.* Courts may have to resolve "contested brute facts," but those factual questions are "subsumed within an already tightly circumscribed legal analysis" and are "part and parcel of the broader legal question." *Id.* at 1680.

The Supremacy Clause "establishes that federal law 'shall be the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary

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[50] *Id.* at 584.

[51] Whether the evidence would have been material to the FDA is a question for the Court to decide. *Albrecht*, 139 S. Ct. at 1679–80.

[52] Lawrence Goldkind, M.D. Deposition Tr. (May 28, 2015) at 80:15–88:23 (attached as Ex. AG to Boehm Decl.).

notwithstanding.'" *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2577 (2011) (ellipsis in original) (quoting U.S. Const. art. VI, cl. 2). "This means that when federal and state law conflict, federal law prevails and state law is preempted." *Knox v. Brnovich*, 907 F.3d 1167, 1173 (9th Cir. 2018) (quoting *Murphy v. NCAA*, 138 S. Ct. 1461, 1476 (2018)). An irreconcilable conflict "arises when compliance with both federal and state regulations is a physical impossibility, or when state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982) (citations and internal quotation marks omitted); *see also Durnford v. MusclePharm Corp.*, 907 F.3d 595, 602 (9th Cir. 2018) ("[FDA] regulations have the same preemptive effect as a statute.").

In failure-to-warn cases involving FDA-approved medicines, plaintiffs must identify "the existence of 'newly acquired information' to support a labeling change under the CBE regulation"—specifically, "data, analyses, or other information ***not previously submitted to the [FDA]***" that "cannot be rooted in conjecture or hypothesis" but rather "must conclusively establish, by scientifically valid measurable and statistically significant data, that the different or increased risks are ***actual and real***,"—or their claims are preempted. *Pradaxa Cases*, No. CJC-16-004863, 2019 WL 6043513, at *3 (Cal. Super. Ct. Nov. 08, 2019) (citing 21 C.F.R. § 314.3(b)); *see also Gibbons v. Bristol-Myers Squibb*, 919 F.3d 699, 708 (2d Cir. 2019) (citing *In re Celexa & Lexapro Mktg. & Sales Practices Litig*, 779 F.3d 34, 41 (1st Cir. 2015) and *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 812 (7th Cir. 2018)) (to state a claim that is not preempted by the FDCA, "a plaintiff must plead a labeling deficiency that [defendants] could have corrected using the CBE regulation"); *McGrath v. Bayer Healthcare Pharmaceuticals, Inc.* 393 F. Supp. 3d 161, 167 (E.D.N.Y. 2019) (holding that newly acquired information "must provide reasonable evidence of a causal association of a clinically significant adverse reaction linked to a drug").

Federal law also preempts state law claims where there is "clear evidence" that

the FDA would "not have approved" a warning plaintiff alleges state law requires. *Wyeth v. Levine*, 555 U.S. 555, 571 (2009); *see Albrecht*, 139 S. Ct. at 1668. "Clear evidence" is not a heightened evidentiary standard. Rather, courts must ask "whether the relevant federal and state laws 'irreconcilably conflic[t].'" *Albrecht*, 139 S. Ct. at 1679 (quoting *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982)).

ARGUMENT

Four years ago, this Court granted defendants' motion for summary judgment based on preemption. Nothing warrants a different conclusion today. The record in favor of preemption has only grown stronger.

Preemption is an issue "for the judge." *Albrecht*, 139 S. Ct. at 1679–80. Accordingly, it is for the Court to determine whether there is clear evidence that the FDA would have rejected a pancreatic cancer warning. Here, it is undisputed that the FDA (i) actively considered the very question at issue in this litigation—whether scientific evidence supports the claim that incretin-based therapies cause an increased risk of pancreatic cancer—and (ii) concluded, based on an unprecedented, comprehensive review of data from multiple sources, that a ***pancreatic cancer risk is unsubstantiated*** and the current ***labeling is adequate***. As this Court previously recognized, "an indeterminate causal association falls below the federal regulatory standards required for labeling changes."[53]

Meanwhile, in the years since the FDA published its conclusions in the *New England Journal of Medicine*, the FDA has continued to approve incretin-based therapies as well as to review and approve more than 50 labeling changes to the products at issue in this MDL, always without requiring a pancreatic cancer warning.

I. There is Clear Evidence the FDA Would Have Rejected Pancreatic Cancer Warnings in the Labeling of Sitagliptin, Exenatide, and Liraglutide.

This Court concluded in 2015 that "the record suggests the FDA's review of pancreatic safety was *more thorough* than a review of relevant data offered in

[53] 142 F. Supp. 3d at 1112.

connection with a CBE or PAS." 142 F. Supp. 3d at 1124–25. Nothing in the updated record warrants a change in that conclusion.

Still, plaintiffs have argued in the past, and may argue again, that preemption is unavailable unless a manufacturer submits, and the FDA rejects, a CBE. Under plaintiffs' theory, the FDA could decide to evaluate specific risk information, publicly announce its intention to conduct an assessment, perform a more robust and comprehensive evaluation of the scientific data about the potential risk than ever before, conclude that the risk is unsubstantiated based on the scientific data, publish those conclusions to the medical community and public in a highly-regarded medical journal—and none of that matters if the manufacturer did not first request a CBE. The Court rejected that argument in 2015.

> [A]lthough Plaintiffs argue a defendant must submit a CBE or PAS to warrant preemption, Plaintiffs do not establish the FDA's substantial review of pancreatic safety was different from what the FDA would have done in response to a CBE. In fact, the record suggests the FDA's review of pancreatic safety was ***more thorough*** than a review of relevant data offered in connection with a CBE or PAS. Instead of reviewing data submitted by an individual manufacturer, the FDA considered a variety of data sources related to the entire class of incretin mimetics. It also conducted its own studies and reevaluated data submitted by manufacturers in reaching its own conclusions. If Defendants *had* submitted a CBE or PAS, which the FDA subsequently rejected, clear evidence would exist and Plaintiffs' claims would be conflict preempted. The facts of this matter are different in form only. ***Although there was no CBE or PAS submission, the FDA conducted an independent review of pancreatic safety and concluded scientific evidence did not support any changes to the product labeling. This is precisely what the FDA would have done upon receipt of a proposed warning by Defendants.***[54]

[54] 142 F. Supp. 3d at 1125 (emphasis added).

Albrecht does not change this analysis, and courts since *Albrecht* have adopted the same reasoning. The Supreme Court expressly stated: "The question of disapproval 'method' is not now before us."[55] The concurring justices in *Albrecht*, just as this Court did, rejected plaintiffs' form-over-substance argument:

> The FDA's duty does not depend on whether the relevant drug manufacturer, as opposed to some other entity or individual, brought the new information to the FDA's attention. Nor does § 355(o)(4)(A) require the FDA to communicate to the relevant drug manufacturer that a label change is unwarranted; instead the FDA could simply consider the new information and decide not to act.[56]

And courts considering the issue of preemption post-*Albrecht* continue to find that clear evidence can exist based on facts other than rejection of a CBE. *See, e.g., Ridings v. Maurice*, No. 15-cv-00020, 2020 WL 1264178, at * 21 (W.D. Mo. March 16, 2020) ("[I]t should not always be the case that simple inaction by the FDA in light of submitted data will always be 'clear evidence' that the FDA would reject a particular warning. In this case, however, in light of the known issues and the ongoing give-and-take between [the manufacturer] and the FDA on these issues . . . the FDA's continued inaction does represent clear evidence under these facts.").

From at least September 2009, the FDA has focused on the pancreatic safety of incretin-based medications.[57] In March 2013, the FDA announced that it would conduct a comprehensive evaluation of a possible association between incretin-based medications and pancreatic cancer and that it would consider the entire body of scientific research and data available to date, as well as the Agency's own "further investigat[ion] [into the] potential pancreatic toxicity associated with the incretin mimetics."[58] In that March 2013 statement, the FDA noted that it would "evaluate all

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[55] *Albrecht*, 139 S. Ct. at 1679.
[56] *Id.* at 1684 (Alito, J. concurring).
[57] *See* Bishai Memorandum (Ex. V).
[58] FDA Review Announcement (Ex. X).

available data to further understand this potential safety issue."[59]

The FDA's February 2014 publication in the *New England Journal of Medicine* reflects the result of its years-long "comprehensive" evaluation—one which included the review and analysis of the FDA's own studies, hundreds of randomized controlled trials, animal data, toxicology studies, spontaneous reports, and more. As plaintiffs' expert Dr. Fleming testified, the FDA's evaluation and publication was "unprecedented" and "reflects a very robust evaluation that went on for a significant period of time."[60]

The FDA's conclusions were unequivocal: "assertions concerning a causal association between incretin-based drugs and . . . pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data" and "the current knowledge is adequately reflected in the product information or labeling." Since that time, as the Court noted in 2015:

> The FDA has also not required any of the Defendants to add a pancreatic cancer warning, or required the inclusion of a warning in newly approved incretin-based therapies. While FDA inaction is insufficient on its own to establish preemption, it is highly persuasive given the FDA's comprehensive review of pancreatic safety and ability to mandate a labeling change if it concluded the regulatory standards were satisfied."[61]

This remains true. Since November 2015, the FDA has approved four new incretin-based therapies for treatment of type 2 diabetes, as well as more than 50 label changes to the medications in this MDL, never requiring the addition of a pancreatic cancer warning, notwithstanding its extensive record of attention to the question of pancreatic safety. In addition to rejecting a citizen petition to remove Victoza from the market,[62]

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[59] *Id*. (Ex. X).

[60] Fleming Tr. (Ex. B) at 92:13–92:16.

[61] 142 F. Supp. 3d at 1124.

[62] *See* Public Citizen Letter (Ex. AA); *see also Cerveny v. Aventis, Inc.*, 783 F. App'x 804, 808 n.9 (10th Cir. 2019) (rejecting plaintiffs' argument that, post-*Albrecht*,

the FDA again evaluated pancreatic safety in 2017 in approving a new indication for liraglutide (Victoza). The FDA concluded that "the totality of information available, [including] the additional information provided in LEADER[,] does not appear to substantively alter the original FDA and EMA conclusions" published in the *New England Journal of Medicine*.[63]

After reviewing the FDA's robust review of these products, plaintiffs' regulatory expert effectively conceded there is clear evidence that the FDA would not have approved a pancreatic cancer warning to the labeling of these products:

> Q. Do you agree with me that it would be absurd for the FDA to say, We've looked at all the data, we've done a comprehensive evaluation, we don't think there's any evidence of causal association, but go ahead and add a warning anyway?
>
> A. It would be a little absurd.[64]

This Court can and should find that there is "clear evidence" that the FDA would not have approved the pancreatic cancer warning that plaintiffs' claim is missing from the products' labels. Their failure-to-warn claims are preempted.

II. Plaintiffs' Purported "Newly Acquired Information" Is Not Material to the FDA's Conclusions, Nor Does it Satisfy the Requirements for a CBE.

In 2015, plaintiffs argued that summary judgment should be denied because "newly acquired information" might not have been provided to the FDA that could have altered the Agency's assessment of a pancreatic cancer warning. The Ninth Circuit directed this Court to consider the materiality of that information. The

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only labeling changes sought by the manufacturer can lead to preemption and reasoning that "we see nothing in *Wyeth* or *Albrecht* excluding [the manufacturer] from justifying preemption on [the] basis" of a rejected citizen petition).

[63] FDA June 2017 Briefing Document (Ex. AS) at 133.

[64] Fleming Tr. (Ex. B) at 201:21–202:1; *see also* Rebuttal Expert Report of Lawrence Goldkind at 13 (attached as Ex. AH to Boehm Decl.) ("FDA either makes a determination that cautionary language belongs in the labeling or FDA makes a determination that it does not belong.").

purported "new safety information" from 2015 consisted of the following:

1. A November 6, 2013 preliminary signal assessment performed by Health Canada, the regulatory body responsible for approving and monitoring prescription medications within Canada, pursuant to that country's laws and regulations;

2. "Clinical trial imbalance information" for sitagliptin and liraglutide;

3. Plaintiffs' expert's characterization of an animal study in exenatide; and

4. A "secondary analysis" to a published animal study in liraglutide.[65]

These issues must be considered on a medication-by-medication basis. Still, a few general points are worth noting at the outset.

First, there is no expert (or other) evidence in the record to support the claim that any component of the purported "newly acquired information" would have been material to the FDA;[66] to the contrary, the only evidence in the record concerning materiality of the purported "newly acquired information" is Dr. Lawrence Goldkind's expert testimony that it is cumulative and repetitive of the very safety information the FDA already has considered.[67]

Second, FDA regulations carefully define what information manufacturers should submit to the Agency, and which information may be submitted pursuant to a

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[65] Doc. No. 1219 at 17–21.

[66] Plaintiffs' preemption expert, Dr. Alexander Fleming, made certain claims about materiality in his original report, which this Court struck. Although plaintiffs persuaded the Ninth Circuit to reinstate the stricken sections of Dr. Fleming's report, plaintiffs subsequently decided to withdraw those same sections. In other words, the scope of Dr. Fleming's opinions in this case remain unchanged from when this Court granted summary judgment in 2015. *See* Declaration of Amy J. Laurendeau.

[67] Goldkind Tr. (Ex. AG) at 92:1–95:4, 125:1–133:1.

CBE, precisely to avoid being flooded with cumulative or irrelevant data.[68] Here, the FDA affirmatively undertook a robust and "comprehensive" evaluation of the scientific information relevant to the very question at issue in this litigation—whether incretin-based therapies cause an increased risk of pancreatic cancer. The Agency's "unprecedented" assessment of a possible association between incretin-based therapies and pancreatic cancer included the following:

- The FDA reviewed safety data from more than 200 clinical trials, involving more than 41,000 patients, more than 28,000 of whom used an incretin-based therapy. 15,000 of these participants used an incretin-based therapy for 24 weeks or more; 8,500 for 52 weeks or more. The FDA also considered clinical trial data from large-scale cardiovascular-outcome trials.
- The FDA "re-evaluated more than 250 toxicology studies conducted in nearly 18,000 healthy animals." These studies showed "no findings of overt pancreatic toxic effects." The Agency also found that "drug-induced pancreatic tumors were absent in rats and mice that had been treated for up to 2 years (their life span) with incretin-based drugs, even at doses that greatly exceed the level of human clinical exposure."
- The FDA conducted "independent and blinded examination" of 120 pancreatic histopathology slides.
- The FDA performed independent toxicology studies with exenatide, and the Agency required additional animal studies, designed to the FDA's specifications, from each of the manufacturers in this litigation.[69]

There is no dispute that the FDA devoted concentrated attention to this specific issue and, in doing so, determined what information was material to its conclusions—as it turned out, an extraordinary and "unprecedented" volume of information from a broad array of sources—including additional studies it required of the manufacturers and at least one study the Agency conducted on its own.

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[68] *See* 21 C.F.R. § 314.70.

[69] FDA Assessment (Ex. A) at 795.

1. Sitagliptin (Januvia and Janumet)

Plaintiffs argued in opposition to defendants' 2015 preemption motion that the FDA might not have considered (i) a November 2013 preliminary signal assessment performed by Health Canada and (ii) evidence of a purported "clinical trial imbalance" in the clinical trial data for sitagliptin.[70]

Health Canada Preliminary Signal Assessment. Health Canada's 2013 preliminary signal assessment, whether the FDA has reviewed it or not, cannot reasonably be considered material to the FDA's evaluation of this issue. It also does not amount to "newly acquired information" under FDA regulation. To start, Canada's regulation for the monitoring and labeling of prescription medicines operates under an entirely different set of laws and regulations than those in the United States. The fact that Health Canada might have reached preliminary conclusions different from those of the FDA—based on different governing regulations than those in the United States—does nothing to show that the FDA failed to consider information that would be material under United States law. *See, e.g.*, *Ridings v. Maurice*, No. 15-cv-00020, 2020 WL 1264178, at *17 (W.D. Mo. March 16, 2020) ("Foreign drug labeling is the product of different and distinct regulatory standards and decisions.").

Moreover, Health Canada's preliminary assessment does not constitute "newly acquired information" under FDA regulation for at least three reasons. First, the assessment was preliminary, and therefore cannot rise to the level of reliability and substance necessary to qualify under the definition of "newly acquired information." *See, e.g.*, *McGrath*, 393 F. Supp. 3d at 167 ("[T]he FDA contemplated that the CBE regulation would be used sparingly, noting it 'would not allow a change to labeling to add a warning in the absence of reasonable evidence of an association between the product and an adverse event.'") (quoting 21 C.F.R. § 201.57(c)(6)(i)). As plaintiffs

[70] Doc. No. 1219 at 18–19.

are aware, Health Canada subsequently updated its preliminary report, finding that "***existing data do not suggest a causal relationship*** between incretin-based therapies and the development of [pancreatic cancer]"[71] and—citing directly from the FDA's conclusions in the *New England Journal of Medicine*—"concluded that there is ***not enough evidence*** at this time ***to confirm a link between incretin-based therapies and pancreatic cancer***."[72] In other words, Health Canada agrees with the FDA's conclusion that a causal association is unsubstantiated. There is not, nor has there ever been, a pancreatic cancer warning on the Canadian equivalent of sitagliptin's label.

Second, Health Canada's preliminary assessment did not reveal "risks of a different type or greater severity or frequency than previously included in submissions to FDA." It does not rely on new data at all, but rather involved an assessment of the same data streams encompassed by the FDA's review (clinical trial data, animal studies, spontaneous adverse event reports), only less comprehensive in scope than the FDA's review.[73]

Third, Health Canada's assessment did not conclude, even in preliminary fashion, that there was ***reasonable evidence*** of a causal association between sitagliptin and pancreatic cancer. *See McGrath,* 393 F. Supp. 3d at 167 ("newly acquired information 'must provide *reasonable evidence* of a causal association of a clinically

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[71] A. Beliveau, Health Canada, *Incretin-Based Therapies and the Risk of Pancreatic Cancer*, Canadian Adverse Reaction Newsletter, 24:4 at 1 (Oct. 2014) (attached as Ex. AI to Boehm Decl.) (emphasis added).

[72] Health Canada, *Summary Safety Review – Incretin-based Therapies – Assessing the Potential Risk of Pancreatic Cancer*, Health Canada (Oct. 2016), *available at* https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00126 (attached as Ex. AJ to Boehm Decl.).

[73] Health Canada's preliminary assessment did not involve reevaluation of toxicology slides, the performance and evaluation of its own studies, or consideration of large-scale clinical trial data for other DPP-4I medications. *See* Doc. No. 1166, Ex. 7 (Health Canada Signal Assessment at §§ 3.4–3.5.1, MRKJAN0000928466).

significant adverse reaction linked to a drug.'") (quoting 21 C.F.R. § 201.57(c)(6)(i)) (emphasis in original). Rather, the 2013 preliminary assessment stated only that sitagliptin "***may be associated*** with an increased risk of cancer of the pancreas." Under 21 C.F.R. § 314.3(b), newly acquired information "must conclusively establish, by scientifically valid measurable and statistically significant data, that the different or increased risks are ***actual and real***," rather than "rooted in conjecture and hypothesis." *Pradaxa Cases*, 2019 WL 6043513, at *3; *see also McGrath*, 393 F. Supp. 3d at 167; *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644, 659 (S.D.N.Y. 2017) ("[L]abeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance"); *Supplemental Application Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008) (FDA "would not allow a change to labeling to add a warning in the absence of reasonable evidence of an association between the product and an adverse event."). A preliminary analysis "concluding that it 'remains unknown' whether a drug is linked to a particular adverse reaction or risk or that 'further studies are required to address possible clinical consequences' do[es] not constitute reasonable or well-grounded scientific evidence of 'clinically significant adverse effects' under the CBE regulation. To find otherwise would permit the 'inclusion of speculative or hypothetical risks' absent 'sufficient evidence of a causal association' between the subject drug and the risks associated with the drug's use." *Ridings*, 2020 WL 1264178, at *15 (quoting *Utts*, 251 F. Supp. 3d at 659).

Health Canada's *preliminary* assessment in 2013 indicating the *possibility* of a pancreatic cancer risk—one Health Canada subsequently described as ***not substantiated*** by scientific data—cannot reasonably be considered material to the FDA's conclusions about pancreatic safety of sitagliptin, nor does it qualify as "newly acquired information" under FDA regulation.

"Clinical trial imbalance." In plaintiffs' 2015 opposition to summary judgment, plaintiffs stated that there was a "clinical trial imbalance of 6 to 3" in sitagliptin randomized controlled trials.[74] Plaintiffs argued that "[r]egardless of whether FDA actually had clinical trial imbalance information buried in the thousands of pages of NDA submissions, there is no evidence FDA actually considered the imbalance," and therefore preemption should not have been granted to Merck.[75]

Plaintiffs are incorrect on all counts, and their own statistics expert does not agree. First, the FDA's February 2014 *New England Journal of Medicine* publication reflects that the Agency considered clinical trial data related to sitagliptin, as well as other incretin-based therapies, as part of its comprehensive evaluation. *See* 21 C.F.R. § 314.3(b) ("Newly acquired information" is defined as "data analyses, or other information not previously submitted to the [FDA]" that "reveals risk of a different type or greater severity than previously included in submissions to FDA.").

Second, also in February 2014, the FDA stated that it intended to pay close attention to the results of the TECOS study, a nearly 15,000-patient randomized controlled clinical trial involving sitagliptin. As it turned out, when the study was completed and published in 2015, TECOS showed that pancreatic cancer occurred in ***fewer*** patients taking sitagliptin (9) than taking the placebo (14)—a risk ratio of 0.66 (95 percent confidence interval 0.28, 1.51).[76] In other words, this result demonstrates the opposite of an increased risk; it suggests, if anything, that sitagliptin may have a ***protective*** effect against pancreatic cancer. Plaintiffs' expert statistician, Dr. David

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[74] Doc. No. 1219 at 19.

[75] *Id.* at 19 (citation and emphasis omitted).

[76] Results of clinical studies can be expressed as a point estimate, often a "risk ratio," that approximates the relationship between exposure and disease. 1.0 would indicate no association—that is, rates of disease are the same with exposure and without exposure. A number below 1.0, as with the sitagliptin clinical trial data, indicates a negative association "which could reflect a protective or curative effect of the agent on risk of disease." Fed. Judicial Ctr., Reference Manual on Scientific Evidence 566–67 (3d ed. 2011) (attached as Ex. AK to Boehm Decl.).

Madigan, agreed that TECOS "provide[s] evidence of a protective association" between sitagliptin and pancreatic cancer.[77]

Third, the statistical analyses of sitagliptin clinical trial data performed both in the peer-reviewed medical literature and by experts in this litigation ***uniformly*** show no increased risk of pancreatic cancer. If anything, the data trend in favor of a ***protective*** effect. Plaintiffs' expert, Dr. David Madigan—plaintiffs' only expert who reviewed sitagliptin clinical trial data—found no increased risk:

> Q: Do you agree that point estimate indicates that the sitagliptin randomized controlled trial data are more compatible with a ***decreased risk*** than with an increased risk?
>
> A: The "more compatible" I don't understand. I mean, its – the point estimate is less than 1. So ***the point estimate, in and of itself, is evidence, in this case, of a protective effect***.[78]

Dr. Madigan also testified:

> Q: [Y]ou are not suggesting that this meta-analysis of the randomized control trial data, to a reasonable degree of scientific certainty, establishes that incretin-based therapies cause an increased risk of pancreatic cancer, correct?
>
> A: Correct, ***I'm not***.[79]

Plaintiffs decided not to ask Dr. Madigan to update his 2015 analysis of sitagliptin clinical trials.[80] The only two experts in this litigation who have analyzed the complete set of sitagliptin clinical trial data—Dr. Robert Gibbons and Dr. Andrew Lowy—share Dr. Madigan's conclusion that sitagliptin clinical trial data do not reflect

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[77] David Madigan, Ph.D. Deposition Tr. (Oct. 19, 2015). at 228:21–229:3 (attached as Ex. AL to Boehm Decl.).

[78] *Id.* (Ex. AL) at 168:20–169:3 (emphases added).

[79] *Id.* (Ex. AL) at 123:24–124:5 (emphasis added).

[80] David Madigan, Ph.D. Deposition Tr. (Jan. 29, 2020) at 24:3–24:9 (attached as Ex. AM to Boehm Decl.).

an increased risk of pancreatic cancer and, if anything, trend in favor of a ***decreased*** risk.[81]

In short, there is no "clinical trial imbalance" for pancreatic cancer in the sitagliptin clinical trial data—numerical, statistical, or otherwise. Any suggestion by plaintiffs that the FDA would add a pancreatic cancer warning to sitagliptin's label based on sitagliptin clinical trial data is utterly without support.[82]

The information related to sitagliptin that plaintiffs have advanced as "newly acquired information" is—even cast in its most favorable light—immaterial to the FDA Assessment of pancreatic safety. Moreover, neither Health Canada's preliminary assessment nor the so-called "clinical trial imbalance" qualifies as "newly acquired information" under the FDA's requirements for submitting a CBE.[83]

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[81] *See* Supplemental Expert Report of Robert D. Gibbons, Ph.D. (Dec. 16, 2019) at 4 (attached as Ex. AN to Boehm Decl.); Expert Report of Andrew M. Lowy, M.D. (Dec. 16, 2019) at 18 (attached as Ex. AO to Boehm Decl.).

[82] Even if this Court were to determine that "newly acquired information" related strictly to another medication precluded preemption as to that product, plaintiffs still could not identify "newly acquired information" that either (1) would satisfy 21 C.F.R. § 314.3(b) requirements for submitting a CBE or (2) would be material to the FDA's conclusions about sitagliptin's pancreatic safety.

[83] A purported numerical imbalance based on an incomplete subset of the overall sitagliptin RCT data could not reasonably be considered "newly acquired information" under FDA regulation justifying submission of a CBE. *See, e.g., Gibbons*, 919 F.3d at 708 (under 21 C.F.R. § 314.3(b), newly acquired information "must have reveal[ed] risks of a different type or greater severity or frequency than previously included in submissions to the FDA"); *McGrath*, 393 F. Supp. 3d at 170 ("[T]he FDA contemplated that the CBE regulation would be used sparingly, noting it would not allow a change to labeling to add a warning in the absence of a reasonable evidence of an association between the product and an adverse event.")

2. Exenatide (Byetta)

Plaintiffs argued in opposition to defendants' 2015 preemption motion that Amylin and Lilly failed to provide the FDA with certain re-analyses of animal[84] data that plaintiffs' general causation expert Dr. Clive Taylor performed for purposes of this litigation.[85] But, as discussed in defendants' accompanying Joint Motion to Exclude Plaintiffs' Causation Experts, Dr. Taylor's testimony should be precluded as his methodology, which is no longer used in human pathology, is both flawed and unreliable.[86] Moreover, his analysis adds little if anything to the FDA Assessment, which described that FDA itself had "reevaluated more than 250 toxicology studies conducted in nearly 18,000 healthy animals (15,480 rodents and 2475 nonrodents)."[87] And FDA also had "approximately 120 pancreatic histopathology slides from one of the three sponsor-conducted studies… subjected to *independent and blinded examination* by three FDA pathologists."[88] The FDA even took the extra step of conducting its own animal toxicology studies with exenatide.[89] Plaintiffs can provide no support for the proposition that their expert's re-analysis for litigation purposes should have been reported to the FDA, much less that it would have changed the FDA's own extensive evaluation of the animal data, along with multiple other streams, including over 200 clinical trials, involving approximately 41,000 participants.[90] In every case premised on an alleged failure to warn, plaintiffs presumably will offer some analysis that the warning was inadequate at some point in time; but characterizing a litigant's re-analysis as "newly discovered evidence" to defeat impossibility preemption would turn the standard on its head.

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[84] Specifically, non-human primates.

[85] 142 F. Supp. at 1129.

[86] Defs.' Mem. of Points & Authorities In Support of Mot. to Exclude Plaintiffs' Experts Drs. Betensky, Landolph, Woolf, and Taylor (Argument IV).

[87] FDA Assessment (Ex. A) at 795.

[88] *Id.* (Ex. A) at 795 (emphasis added).

[89] *Id*. (Ex. A) at 795–96.

[90] *Id.* (Ex. A).

Plaintiffs' expert's re-analysis of animal data is hardly the type of material "newly acquired information" warranting a label change. *See McGrath*, 393 F. Supp. 3d at 169–70 (finding single study performed on mice does not constitute newly acquired information); *Utts*, 251 F. Supp. 3d at 663–69 (medical journal articles and independent analysis of adverse event data was not newly acquired information as they did not refer to any new information that would have permitted the defendants to change the drug label); *Roberto v. Boehringer Ingelheim Pharm.*, No. CPL-HHDCV16-6068484S, 2019 WL 4806271, at *19 (Conn. Super. Ct. Sep. 11, 2019) (finding expert testimony unsupported by published research was not newly acquired information).[91] It would be absurd to allow preemption to be defeated by an expert opinion that never was (or would be) submitted to the FDA. As set forth *infra*, the FDA considered hundreds of animal studies and conducted its own analysis of animal data as part of its Assessment, highlighting how animal studies that did not reveal cancer were not material.

On remand, plaintiffs have not come forward with any new evidence and, in fact, have ignored the results of the EXSCEL study, the nearly 15,000-patient exenatide randomized controlled trial, completed in 2017[92] and which the FDA noted in the Assessment had been ongoing.[93] In the EXSCEL trial, pancreatic cancer occurred in **fewer** patients on exenatide (15) than on placebo (16), a result that is inconsistent with exenatide use being associated with pancreatic cancer and wholly inconsistent with the Dr. Taylor's interpretation of the the animal data. At his 2020 deposition, Dr. Madigan testified that he has never even looked at the EXSCEL

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[91] As Dr. Goldkind testified, "I can't conceive of a, of an animal study that could, could change the weight of evidence of 240 studies and dozens of two[-year] carcinogenicity studies on multiple animal species, I can't conceive [of] that." *See* Ex. AG at 112:17–113:1.

[92] Rury R. Holman, et al., *Effects of Once-Weekly-Exenatide on Cardiovascular Outcomes in Type 2 Diabetes*, N. Engl. J. Med. 377:1228 (Sept. 2017) ("EXSCEL study") (attached as Ex. AP to Boehm Decl.).

[93] *See* FDA Assessment (Ex. A).

paper.[94] Moreover, plaintiffs' newly designated biostatistics expert, Dr. Martin Wells, testified that including the EXSCEL results in his analysis of exenatide clinical trials yielded a result for pancreatic cancer that is "consistent with no increased risk."[95] Thus, far from supporting the addition of a pancreatic cancer warning for exenatide, plaintiffs' purported "newly acquired information" is consistent with the FDA's conclusion in the Assessment that a label change to add a pancreatic cancer warning is not warranted.[96]

3. Liraglutide (Victoza)

In 2015, plaintiffs argued that Novo did not provide the FDA with the results of a post-hoc,[97] exploratory analysis of rat tissue that attempted to look at the effect of liraglutide treatment on a normal compartment of the pancreas, known as pancreatic duct glands (PDGs). That is true. Although the results of the primary study were published and shared with the FDA, Novo did not submit the post-hoc PDG analysis to the FDA. Dr. Knudsen, the lead Novo researcher on the study, explained at her deposition that the results of the post-hoc analysis never were finalized, published, or

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[94] *See* Madigan 2020 Tr. (Ex. AM) at 207:1–207:6, 234:16–234:22.

[95] *See* Martin T. Wells Deposition Tr. (Jan. 22, 2020), at 77:4–77:19 (attached as Ex. AQ to Boehm Decl.). Defendants simultaneously are moving to preclude Dr. Madigan's and Dr. Wells's testimony on *Daubert* grounds, as their opinions are dependent on a result-driven methodology that relies on unqualified and unscientific cherry-picking of studies. Defs.' Mem. of Points & Authorities In Support of Mot. to Exclude Plaintiffs' Causation Experts Drs. Madigan, Wells, Brown and Gale (Arguments I(A) – (B)).

[96] Even if this Court were to determine that "new safety information" related strictly to another medication precluded preemption as to that product, plaintiffs still could not identify "newly acquired information" that either (1) would satisfy 21 C.F.R. § 314.3(b) requirements for submitting a CBE or (2) would be material to the FDA's conclusions about exenatide's pancreatic safety.

[97] A post-hoc analysis refers to a subsequent analysis performed on a data set that has already been collected and analyzed for primary outcomes.

shared with the FDA because it was a failed analysis, *i.e.*, its significant limitations precluded making any reliable conclusions.[98]

Defense expert Dr. Sarah Thayer agreed. Dr. Thayer is one of the scientists who first identified PDGs in the pancreas, which she describes as "unique structures in the normal exocrine pancreas that retain expression of developmental markers . . . and are a site of productions of gastric-type mucins."[99] She exhaustively reviewed the nearly 2,000 digital slides created as part of the analysis and reviewed the draft study report. [redacted][104]

In June 2017, the FDA summarized its review and analysis of the animal studies evaluating the pancreatic safety of liraglutide and other incretin-based

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[98] Lotte Knudsen, M.D. Deposition Tr. (Sept. 12, 2019), at 172:8–172:10 (attached as Ex. AR to Boehm Decl.).

[99] Expert Report of Sarah Thayer, M.D., Ph.D., (Dec. 16, 2019), at 20 (attached as Ex. AT to Boehm Decl.).

[100] *Id.* (Ex. AT) at 21.

[101] *Id.* (Ex. AT).

[102] *Id.* (Ex. AT).

[103] *See id.* (Ex. AT).

[104] *Ridings*, 2020 WL 1264178, at *18 (W.D. Mo. Mar. 16, 2020); *see also McGrath* 393 F. Supp. 3d at 169-70 (E.D.N.Y. 2019).

medications and reiterated that the medications do not appear to have any over pancreatic toxicity:

> An evaluation of nonclinical assessments supporting marketing applications for incretin-based drugs by the FDA and the European Medicines Agency that included more than 250 toxicology conducted in approximately 18,000 healthy animals (15,480 rodents and 2,475 nonrodent mammals) showed no overt pancreatic toxicity or pancreatitis (Egan 2014). In lifetime rodent carcinogenicity studies, there were no incretin-based drug-related pancreatic tumors in mice or rats, even at high multiples of human exposure. FDA also required sponsors of marketed incretin-based drugs to evaluate pancreatic toxicity in 3-month studies in rodent models of T2DM, and no drug-related adverse effects were reported, including the study of liraglutide in ZDF rats conducted by Novo Nordisk to satisfy a nonclinical postmarketing requirement. In the absence of overt pancreatic injury from incretin-based therapies in healthy animals or rodent models of T2DM, the FDA no longer routinely requires sponsors developing incretin-based therapies to perform dedicated pancreatic safety studies in rodents.[105]

Considering the scope of evidence considered by the FDA, it is beyond the pale to believe that the Agency would change its ultimate conclusions based on *inconsistent findings* regarding proliferation of normal cells, generated *from a single post-hoc analysis* of a study *that found no pancreatic cancer, no pre-cancerous lesions, and no overt pancreatic toxicity* in rats treated with liraglutide. Certainly, neither plaintiffs nor their experts have provided any basis for the Court to make such inference. Tellingly, none of plaintiffs' causation experts cited the PDG analysis of rat tissue in their reports or even mentioned it at their deposition.

No amount of cherry-picking of study findings by plaintiffs' counsel, or allegations about what the FDA might do with some specific piece of animal data, can alter what the FDA actually has done and continues to do to this day. Over the past

[105] FDA June 2017 Briefing Document (Ex. AS) at 20–21.

decade, the FDA has reviewed results from hundreds of pre-clinical studies, dozens of clinical trials (including LEADER in humans), and numerous observational studies (in humans, taking liraglutide under real-world conditions).[106] As with any large body of data, imbalances occasionally were seen in studies (some favoring incretins and some not) and pathologic findings rarely were observed in some animals.[107] The FDA has followed this data as it accumulated over time and consistently has concluded that the totality of evidence does not support (1) a causal relationship between liraglutide (and

[106] Based on plaintiffs' questioning of Novo fact and expert witnesses, Novo expects plaintiffs also will argue that the results of the Humedica study represent "new safety information" that would have altered the FDA's conclusion. The Humedica study was an observational study that attempted to assess the incidence of pancreatic cancer in a population of patients who had type 2 diabetes and had risk factors similar (at least to some extent) to those in LEADER. The study ***did not*** evaluate pancreatic cancer risk with liraglutide, and none of the patients included in the study actually took the medication. Plaintiffs' own expert, Dr. Madigan, declined to rely on the Humedica data for his opinion, noting that any attempt to compare the incidence rates in Humedica to those in LEADER would be highly problematic: "So are there limitations with such comparisons? You betcha there are, and I'm not considering there are. I'm just observing, you know, how it turned out." (Madigan 2020 Tr., Ex. AM, at 80:12–80:17; 198:8–198:21).

[107] Novo similarly expects plaintiffs to argue that incidental pancreatic findings in certain animal studies suffice as "new safety information." These isolated findings in rats and mice in studies not designed to assess pancreatic safety are not evidence of a treatment effect. Indeed, it is well-recognized there is a significant background rate of pancreatic findings in rodents, without any exposure to incretin-based therapies. *See* K. Chadwick, et al, *Occurrence of Spontaneous Pancreatic Lesions in Normal and Diabetic Rats: A Potential Confounding Factor in the Nonclinical Assessment of GLP-1–Based Therapies*, Diabetes 63(4), 1303–14 (Apr. 2014) (attached as Ex. AU to Boehm Decl.). Moreover, none of the animals in these studies developed pancreatic cancer or even pre-cancerous lesions. As such, the "new safety information" plaintiffs may identify in their opposition does not provide any evidence to suggest Victoza causes pancreatic cancer, nor could it reasonably provide a basis for the FDA to alter the findings of its comprehensive and continuous assessment of the pancreatic safety of incretin-based therapies.

other incretin-based medications) and pancreatic cancer or (2) "incorporation of changes regarding the potential pancreatic cancer signal in product labeling."[108]

The FDA has put this conclusion into action by approving additional incretin-based therapies and expanding indications for existing medications without including any information regarding pancreatic cancer in the labeling. In particular, in August 2017, the FDA approved an additional cardiovascular risk reduction indication for Victoza, and in June 2019, approved use of Victoza in pediatric patients 10 years old and over, making liraglutide, an incretin-based therapy, the first non-insulin drug approved to treat type 2 diabetes in children since 2000.[109] The FDA did so after conducting a thorough review of the pancreatic safety of liraglutide in 2017 and without including any information on pancreatic cancer in the labeling, again underscoring the pancreatic safety of these therapies. Considering this history and the FDA's labeling mandate under FDAAA, it is clear that the FDA would not approve a pancreatic cancer warning for liraglutide or for any other incretin-based therapy. "FDA's continued inaction does represent clear evidence under these facts."[110]

CONCLUSION

The FDA has been focused for many years on the central question at issue in this litigation—whether the labeling for defendants' drugs should include a pancreatic cancer warning.[111] It is and has been the FDA's position that the scientific evidence does not support a pancreatic cancer warning, and there is clear evidence that the FDA would reject the addition of such a warning pursuant to its regulatory requirements.

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[108] FDA June 2017 Briefing Document (Ex. AS) at 129.

[109] *See* FDA Label Updates for Victoza, dated June 2019 (Ex. AC); *see also* Ex. AF.

[110] *Ridings*, 2020 WL 1264178, at *21 (W.D. Mo. Mar. 16, 2020) (emphasis in original).

[111] Fleming Tr. (Ex. B) 122:23–123:1 ("Q: Dr. Fleming, do you agree that the FDA has closely monitored a potential signal for pancreatic cancer for several years now? A: Yes.").

For the reasons set forth above, defendants respectfully request that this Court grant summary judgment on all counts on the basis of conflict preemption.

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Respectfully submitted,

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